Claims 3 and 12 have been objected to for typographical errors, which have now been corrected in the foregoing amendments.

Claim 5 has been rejected for being indefinite. The rejection has been rendered moot by the foregoing amendment.

Claims 1-3, 5 and 11-16 are held rejected under 35 U.S.C. § 112, 2nd ¶ as being indefinite. The first issue relating to the alleged indefiniteness of the term "SOD mimics" is now moot in view of the foregoing amendment. However, the amendment is not to be construed as Applicants' conceding the correctness of the rejection. The Applicants still maintain that one with ordinary skill in the radical scavenging arts clearly understands what comprises "SOD mimics."

The second indefiniteness issue is that the Examiner believes that the "difference between hydrogel and PEG" is unclear. Office Action, page 4, item 6. The Examiner then notes that Applicants did not incorporate the claim proposed in the Office Action of November 26, 2001.

In response, the Applicants, at first, apologize for inadvertently not responding to this suggestion in the last response. That said, it is the Applicants' position that there is no confusion and that one with skill in the art would have no problem distinguishing between the terms *hydrogel* (the invention) and *PEG* (a component of the hydrogel), as disclosed in the specification. Further, as will become evident, the Examiner's proposed amendment was not incorporated because it does not accurately describe the invention. Accordingly, the Applicants briefly describe invention.

Claim 1 (amended twice), begins "A hydrogel comprising...." There should be no doubt that the invention is a *hydrogel*. Further, the hydrogel is formed from, i.e., *comprising*, a combination of certain components. The components, comprise *biomolecules* and *PEG*. In equation form, hydrogel = biomolecules + PEG.

The specification aptly describes the type of hydrogel claimed herein, e.g., bottom of page 2, continuing to the top of page 3.

Applicants' hydrogel is disclosed in the 4th ¶ of page 3 – hydrogel comprising a protein or enzyme and PEGs. Taken together, protein containing hydrogels are matrices of (1) polymerized and crosslinked PEGs, to which (2) proteins are attached. Applicants express their good faith belief that there is no apparent basis for Examiner's

perception (or one with skill in the art) that *hydrogels* and *PEGs* are equivalents, or somehow not distinguishable.

Page 15 of the specification outlines a proposed method of forming the hydrogel. Accordingly, the Applicants respectfully suggest that the specification clearly distinguishes hydrogels and PEGs sufficiently so as to render the claims definite to those with skill in the art.

Viewed in this context, Examiner's proposed claim does not capture the essence of the invention. The claimed hydrogels are not merely *compositions* comprising PEG molecules, but *structures* that comprise crosslinked PEGs and, differ from the art in manner by which active proteins are attached to the formed insoluble PEG matrix.

Applicants respectfully request that the indefiniteness rejection be withdrawn in light of the foregoing discussion.

THE COMBINATION OF FORTIER AND GALIN DO NOT RENDER THE CLAIMS OBVIOUS

The Applicants' hydrogel is nonobvious over Fortier's because, *inter alia*, it allows the direct attachment of enzymes that may be useful in promoting wound healing. Such enzymes include, but are not limited to, free-radical scavengers, proteolytic enzymes, lipases and various other esterases and hydrolases capable of digesting necrotic flesh, scar tissue, wound debris, and also aid in tissue remodeling during wound healing.

As discussed below in detail, Fortier requires that albumin be present. Without albumin, other enzymes that Fortier tested, simply washed off the PEG matrix during preparation because they were not securely attached. This means that Fortier's method does *not readily permit many important proteins to become directly attached to the PEG matrix of the hydrogel.* In contrast, the Applicants' hydrogel and method of preparation allow direct attachment of virtually any protein in the absence of albumin.

From a practical standpoint, this means that albumin can be totally omitted. Therefore, on a per unit weight of hydrogel basis, there will be attached many *more types of therapeutically useful proteins.* Albumin is a serum protein used

commonly in research, but it known not to have any enzyme activity. Accordingly, many if not most applications would benefit from albumin not being part of the hydrogel.

For example, many of the proteins sought to be attached are proteolytic enzymes. Thus, Fortier's requirement for the presence of albumin would likely render Fortier's hydrogel completely useless for this purpose. This is because requiring the attachment of albumin (a protein) is equivalent to requiring *competitive inhibitors* of most proteases to be in contact with the therapeutic proteases. Thus, Applicants' improvement provides a substantial benefit to this art.

Thus, chemically, structurally and functionally, the Applicants' hydrogels are distinct and nonbvious from Fortier.

This is true, even when Fortier is combined with Galin.

A. Fortier EXPRESSLY Teaches Away From Applicants' Claimed Invention and Cannot Render the Claims Obvious

I. Fortier Teaches Away From The Claimed Invention

Applicants' respectfully suggest that a *prima facie* case of obviousness cannot be justly predicated on Fortier's disclosure.

In ascertaining whether claims are obvious over cited references, the references "should be considered as a whole, and portions arguing against or teaching away from the claimed invention must be considered." Bausch & Lomb, Inc., v. Barnes-Hind/Hydrocurve, Inc., 230 USPQ 416 (Fed. Cir.1986).

Teaching away arises when "a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re* Gurley, 31 USPQ2d 1130 (Fed. Cir.1994).

In the present case, Fortier teaches that his hydrogel requires bovine serum albumin (BSA) whenever a non-BSA protein, e.g., an enzyme or radical scavenging, is to

be incorporated into the hydrogel. *See* Fortier, column 14, lines 51-67. In this passage, Fortier discloses that attempts to attach enzymes *without* first attaching BSA to the PEG matrix, led to re-dissolving the hydrogel. He states the conclusion as follows:

> This example clearly demonstrates the unexpected important role of albumin protein in maintaining the integrity of the hydrogel structure. Consequently, albumin plays a key role as a co-protein of reticulation, avoiding the redissolution of the hydrogel.

See column 14, lines 59-64.

The Applicants clearly disclose this key drawback in Fortier's hydrogel as a major problem in the art. *See* specification, page 2, last paragraph, to page 3, second paragraph. The Applicants further disclose that Fortier could *only* achieve immobilization of oligomeric enzymes by forming a ternary complex having the general structure, PEG–BSA–enzyme. Specification, page 17, second paragraph.

This is completely contrary to the Applicants' invention. For example, the Applicants conclude:

> It has further emerged, surprisingly, that the described form of PEG activation via diisocyanates permits immobilization of proteins and enzymes **other than albuminoid ones...."**

Specification, page 17, lines 11-13. (Emphasis added).

In support of their conclusion, Applicants provide several illustrative experiments in which various albumin-free hydrogels are prepared. The examples are only presented as a means to illustrate that a core distinction between the Applicants' invention and Fortier, without intending to limit the claims' scope. Several exemplified hydrogels are shown to incorporate active enzymes in the absence of albumin. *See*, Examples 2-8.

In view of these contrasting disclosures, one with ordinary skill in the art could not use Fortier's teachings to arrive at the Applicants' claimed hydrogel. In view of Fortier, the skilled artisan would necessarily be discouraged from attempting to create an albumin-free hydrogel. Thus, the foregoing facts fall squarely under the rule of

Gurley, and reveal that Fortier clearly and expressly teaches away from the Applicants' claimed subject matter.

On this basis alone, Examiner would be completely justified in withdrawing the rejections.

II. Galin Does not Cure the Deficiencies in Fortier's Disclosure

The contrary nature of Fortier's disclosure by itself is sufficient to overcome the rejection under § 103(a). However, even combining Fortier with Galin does not remedy Fortier's contrary teachings. One reason is that., as disclosed in the cited abstract, Galin's PEG polymer cannot be used in the Applicants' claimed compositions, because the urethane groups were *blocked*. *See*, Abstract, last line on first page.

It is precisely these urethane groups that are required for the attachment of proteins to the PEG matrix. *See* page 3, 4th ¶. There cannot be any reasonable expectation of success in attaching proteins to these urethane groups if they are blocked. One may conclude that all diisocyanate crosslinkers are not equivalent, and do not provide equal expectations of success.

Therefore, Galin directly contradicts the Examiner's conclusion that "*Galin has shown success in activating PEG with diisocyanate by creating CO-NH residues*" that can bind to proteins, enzymes, etc. *See* Office Action of November 26, 2001, page 7. Respectfully, we point out that Galin has shown nothing of the kind. Further, the blockage of the urethane groups supports the conclusion that Examiner incorrectly equates Galin's covalent attachment of the diisocyanate to PEG, to an "activation" *within the meaning of the instant invention.*

In fact, Galin has not "activated" anything. There is no disclosure that the PEG has been "activated" to a form any suitable structure for *any practical purpose* other than to create the lamellar structures that are the subject of Galin's studies.

III. Combining Galin and Fortier Constitute Impermissible Hindsight Reconstruction of the Claims

By combining Galin with Fortier, the Examiner has merely used the claims and the specification against Applicants by using them as a blueprint or template to reconstruct by hindsight, a mosaic of Applicants' claim limitations. This is not a proper mode of analysis. Sensonics, Inc. v. Aerosonic Corp., 38 USPQ2d 1551 (Fed. Cir. 1996) ("To draw on hindsight knowledge of the patented invention, when prior art does not contain or suggest that knowledge, is to use the invention as a template for its own reconstruction – an illogical and inappropriate process by which to determine patentability.")

In order for Galin to sufficiently complement Fortier and thus, provide a legally sufficient disclosure that even remotely resembles the Applicants' claims, Galin must provide sufficient guidance such that one with ordinary skill would have a reasonable expectation of success using 2,4–toluene diisocyanate-modified PEG to produce *albumin-free hydrogels bearing catalytically active enzymes.*

Galin does not provide any of such guidance, and Fortier indicates that Applicants' hydrogel is not plausible.

Galin merely discloses a polymer formed of 2,4–toluene diisocyanate-modified PEG. The abstract merely refers to crystallization temperature and lamellar thickness in qualitative terms.

However, Galin does not disclose:

(1) the desirability of forming a hydrogel or using their PEG-polymer as a matrix for preparing a hydrogel;

(2a) the desirability of their 2,4–toluene diisocyanate-modified PEG as a substitute for Fortier's use of nitrophenyl chloroformate to obtain PEG dinitrophenyl carbonates;

(2b) and that Galin's modified PEG would be suitable for covalent attachment of any protein, let alone active enzymes, into the hydrogel matrix;

(3) the resultant polymer's use for linking with proteins even in the absence of an albumin-type protein;

(4) methodology for attaching an oligomeric enzyme and retaining its catalytic activity.

To establish a *prima facie* case of obviousness there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant"s disclosure. *In re* Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). See MPEP § 2143 - § 2143.03.

In view of Galin's total lack of any suggestion to make any therapeutic use of their lamellae, let alone attach active proteins to it, it appears that the Applicants' disclosure was used as a blue print to combine the references. As stated in *Vaeck*, this is an inappropriate basis to reject the claims.

Accordingly, the Applicants respectfully solicit withdrawal of the rejections under § 103(a).

B. The Examiner Improperly Ignored Applicants' Unexpected SuperiorResults

In the Office Action of February 15, 2002, attention was drawn to Figure 1 of both of Fortier and Applicants. This shows the gelling rate of their respective hydrogels. Applicants' hydrogel gelled at a rate that was approximately ***60-fold*** more rapid than Fortier's. This comprises objective evidence that the two compositions *cannot reasonably be considered equivalent or even similar*. Further, this is clearly superior and unexpected results in view of the fact that there is *no suggestion of any modification in Fortier or Galin that would yield a 60-fold faster gelling rate.*

"A greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness...of the claims at issue." *In re* Corkill, 226 USPQ 1005 (Fed. Cir. 1985). In addition, showing that the claimed composition is superior in a property shared with the cited composition, can be enough to rebut *prima facie* case of obviousness. MPEP § 716.02(a).

The gelling assay is a convenient method for determining when a gelled matrix becomes *insoluble* in a solution. Thus, a substantial portion or perhaps even a majority of the gelling has occurred at that point. It is also known in the art that after this point is reached, further polymerization may occur.

However, rather than view this evidence as a clear and objective demonstration of the lack of similarity between Applicants' hydrogel and that of Fortier, Examiner disregarded the evidence, and read in her own interpretation. This mode of analysis is in clear violation of PTO guidelines and established case law requiring that all objective evidence be considered. MPEP § 2444.05. Instead, Examiner marginalizes the evidence by substituting her own subjective analysis, rather than provide objective evidence or reasoning. This is clearly improper

Specifically, Examiner expresses "confusion" because page 25 of the specification states that "complete crosslinking of the hydrogel occurs after 12 h of storage at room temperature." Final Action, page 6, last paragraph. Examiner then states that, "it is not clear how this 12 h of complete reaction time is superior to those reported by Fortier which are of the order of 2 h."

In making this statement Examiner must have concluded that 12 h is required for Applicants' hydrogel to reach complete gelling ***and*** that Fortier's requires only 2h. There is not a single piece of objective evidence offered to support this conclusion. Simply because Fortier does not discuss the conditions he uses to ensure

100% gelling, it is improper to read into Fortier that complete gelling was achieved at 270 minutes, *absent any objective esupporting evidence.*

What is the basis for Examiner to conclude that at Applicants' gelling point in Figure 1, the hydrogel is *incompletely* gelled, but at Fortier's gelling point it is 100% gelled? Because Fortier does not disclose any further relevance to these results and does not provide a further analysis. No evidence supports Examiner's conclusion. Thus, this line of reasoning is clearly insufficient to rebut the objective evidence of unexpected results.

Similarly, one may ask how does Examiner know that Fortier's complete gelling time does not require 24 hrs, or 48 hrs?

How can one know whether the Applicants' hydrogel is 80% gelled at 300 seconds, but that Fortier's is only 20% gelled at 270 minutes?

It is clear that upon this record, we cannot resolve the above-stated issues. All that is objectively ascertainable, is that the objective tests show that Applicants' PEG reaches its gelling point 60-times faster than does Fortier's, and it does so at several pH's. On this record, Applicants' hydrogels are clearly ***prima facie nonobvious***, and the rejections over Fortier and Galin should be withdrawn.

From a practical perspective, a less than completely gelled hydrogel may be useful in emergency situations, where requiring hours for gelling to take place is of no value. By then, the injured party would likely be in the hospital. Thus, for effective first-aid treatment, there can be little doubt that the 60-fold more rapid gelling time is of major practical significance and constitutes an unexpectedly superior result.

CONCLUSION

Reconsideration of the application in view of the amendments and remarks are respectfully solicited.

In view of some apparent confusion related to the nature of the invention, the Applicants have described the hydrogel in detail and have clearly described the distinguishing features.

The Applicants' have also indicated that the combination of Fortier and Galin are insufficient to render the claims obvious. This is based on three facts: (1) Fortier teaches away from the claims by requiring that albumin always must be present when conjugating non-albumin proteins; (2) Applicants' have demonstrated unexpected and superior results compared to Fortier; and (3) that Galin cannot remedy Fortier's contrary teachings.

It is respectfully requested that the rejections of claims 1-3, 5 and 11-16 under 103(a) be withdrawn.

Respectfully submitted,

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MARK-UP OF AMENDED CLAIMS

Claim 1 (Amended three times). A hydrogel comprising

at least one protein or peptide ~~biomolecule chosen from the group consisting of proteins, enzymes, SOD/catalase enzyme mimics,, and recombinant proteins and enzymes,~~ linked via urea groups to PEGs, and wherein said protein or peptide is capable

Claim 3 (Amended three times).The hydrogel according to Claim 1, wherein the PEGs are activated by aliphatic or aromatic ~~oraromatic~~ or ~~araliphatic~~ arylaliphatic diisocyanates.

Claim 5 (twice amended). The hydrogel according to claim ~~Claim~~ 1, wherein free radical scavengers are selected from the group consisting of superoxide dismutase, catalase, glutathione peroxidase, myeloperoxidase, ~~SOD/catalase enzyme mimics~~ and combinations thereof ~~are used as proteins~~.

Claim 12 (twice amended). A process for producing a hydrogel according to ~~Claim~~ claim 1, comprising ~~Comprising~~ the steps of, in order:

a) reacting anhydrous PEGs with diisocyanate in a solvent, optionally in the presence of a catalyst,

b) removing the solvent from the resulting product of activated PEGs by filtration, washing or drying,

c) reacting the activated PEGs in aqueous solution with proteins, theproteins being present in a buffer which is optionally chosen so that theproteins retain their biological activity,

d) optionally, carrying out purification steps and washes .